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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/122,588	07/23/98	SEMPLE S	016303-00531

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TOWNSEND AND TOWNSEND AND CREW
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EXAMINER	
SCHMIDT,M	
ART UNIT	**PAPER NUMBER**
1635	7

DATE MAILED: 05/27/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/122,588	Semple et al.
Examiner	**Group Art Unit**
Schmidt	1635

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disp sition of Claims

☒ Claim(s) 1-61 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-61 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6

☐ Interview Summary, PTO-413

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

Other _____

Office Acti n Summary

DETAILED ACTION

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth: the application contains the sequence of a VEGFR ribozyme which is not identified by a sequence identifier. To be in compliance with the rules, the sequences in the instant application need to be assigned sequence identifiers and submission of paper listings of the sequences as well as a computer readable form are required.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."

Claims 17-20 are rejected under 35 U.S.C. 101 since the claimed invention is directed to non-statutory subject matter. The terminology used in these claims for cells containing nucleic acid molecules, encompasses cells as implanted in a human or in a human who has been made transgenic by the presence of such constructs. Claims directed to or including within its scope a human (e.g. a human with the cellular material) will not be considered patentable subject matter

under 35 U.S.C. 101. The grant of a limited, but exclusive property right of a human being is prohibited by the Constitution. See 1077 OG 24.

Claim Rejections - 35 USC § 112

3. Claims 1, 15, 21, 26, 36, 39, 46, 50, and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 26, 50, and 61 contain the language "proportions sufficient to achieve said delivery" or "conditions suitable for the transfer of said nucleic acid catalyst" which is indefinite because the metes and bounds of such proportions or conditions are not clearly defined in the specification as filed. It is not clear whether they refer to the actual amount of liposome (and the amounts of the individual components thereof) or the method of delivery to a cell or a whole organism (such as injection, incubation, etc.) or the ability of the liposome to actually enter a target cell (*in vitro* or *in vivo*).

Claim 15 contains a typographical error, "chorine" should read "choline."

Claim 21 contains the language "capable of" which is indefinite because it merely describes a latent characteristic of the catalyst, the scope of which is unclear. The definite language "which" or "is" is suggested to more clearly define the invention.

Claim 36 is indefinite for the language "cleaved RNA encoded by... RNA" because RNA does not 'encode' another RNA. It appears the claim should state that the RNA to be cleaved is VEGF-R RNA.

Claim 39 contains the language "a merger nucleic acid molecule" the scope of metes and bounds of which is unclear. Does "merger" refer to any nucleic acid target molecule which binds or otherwise interacts with the catalytic molecule in order to be cleaved?

Claim 46 is indefinite for description of the catalyst as "represented by a plasmid." It is not clear how such language defines the characteristics of the catalyst and plasmid or what the relationship between the catalyst and the plasmid encompass. For instance, does "represented by" refer to expression of the catalyst from an expression vector? Claim 46 also contains a typographical error, "ia" should read "in."

Claim 50 lacks antecedent basis for "said method" because the preamble recites "a composition."

4. Claims 1-15, 17-20, 26, 35-37, 39-46, 49-59 and 61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cells and methods of delivery and/or treatment involving the liposome containing a catalytic nucleic acid *in vitro*, does not reasonably provide enablement for application of such compositions to any biological system including any whole organism or cells there of. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-15, 35-37, 40-59 and 61 are drawn to compositions for facilitating delivery of a nucleic acid catalyst to a biological system. The compositions comprise a PEG-ceramide conjugate, a lipid, and a nucleic acid catalyst. Dependent claims 2-4 further comprise, a phosphatidyl choline, cholesterol, or both. Claims 5-8 specify the nucleic acid having endonuclease activity, comprising one or more ribonucleotides or deoxyribonucleotides, or a hammerhead motif. Claims 9 and specify the lipid as DODAC or DOTAP. Claims 12-14 and 49 specify the PEG-Ceramide conjugate as a fatty acid of 8, 14 or 20 carbons, or between 6 and 20 carbons (claim 49). Claim 15 specifies the phosphatidyl choline as egg yolk phosphatidyl choline.

Claim 35 specifies a chemically modified catalyst. Claims 36-37 are drawn to a catalyst for cleaving VEGF-R RNA such as VEGF-R-1. Claims 40-41 specify formation of the compositions of claims 1-4 via a reverse phase evaporation process or the Bligh and Dyer extraction method. Claims 42-44 specify the concentrations of the lipid as 0-30%, 5-30%, or 15%. Claim 45 specifies 50% egg yolk phosphatidyl choline, 25% cholesterol, 15% lipid, and 10% PEG-Ceramide conjugate. Claim 46 specifies the nucleic acid catalyst encoded by a vector. Claims 50 and 61 further specify a composition having a PEG-Cer, phosphatidylcholine, cholesterol and nucleic acid catalyst or a non-cationic lipid, a cationic lipid, PEG-Cer and nucleic acid catalyst.

Claims 17-20 are drawn to mammalian cells, such as human cells, containing the compositions of claims 1-4. Claim 26 is drawn to a method of facilitating the transfer of a nucleic acid catalyst into a cell via contacting the cell with the composition of claims 1-4 under suitable conditions for transfer. Claim 39 is drawn to a method of cleaving a merger nucleic acid molecule in a cell via application of the composition of claim 5.

The specification teaches delivery of liposomes made by method (2) (EPC-DOTAP:PEG) or ribozymes in saline (non-formulated) via intravitreal injection to mice. The specification further teaches EYPC(egg yolk PC):DOTAP-PEG C8 liposome delivery. The specification further teaches preparation and delivery to mice of EPC:CHOL (55:45), Shingomyelin (SM):EPC:CHOL (33:33:33), and EPC:CHOL:DODAC:PEG-Ceramide-C20 (50:25:15:10) (see Figure 9). Example 5 teaches the following formulations synthesized via method (1): EPC:CHOL:DODAC:PEG-ceramide-C20 (50:25:15:10), EPC:CHOL:DODAC:PEG-ceramide-C8 (50:25:15:10) and EPC:CHOL for injection into mice.

Claims 1-15, 17-20, 26, 35-37, 39-46, 49-59 and 61, read on application of the ribozyme-liposome compositions to any biological system or mammalian cell which reads on application to whole organisms.

Construction of liposomes for optimal introduction of nucleic acids into culture cells is well known in the prior art. There is a high level of unpredictability however for applications of such liposomes to whole organisms. The factors considered unpredictable in a whole organism

are: (1) drug leakage from the liposome, (2) hydrolysis of the liposome, (3) uptake of the liposome by the RES system or other undesired immune responses, (4) targeting the liposome to the desired tissue(s) or cell(s), and (5) delivery of the drug into the cell and further success of the delivered drug. For instance, see Templeton et al. who teach "although efforts to synthesize new cationic lipids has led to the discovery of more efficient transfection agents, their efficiency measured in cultured cells does not correlate with their ability to deliver DNA after systemic administration in animals. Functional properties defined *in vitro* do not assess the stability of the complexes in plasma or their pharmacokinetics and biodistribution, all of which are essential for activity in vivo (p. 647, first para.)."

In the instant case the claims are drawn to delivery of a ribozyme-liposome complex into a biological system which reads on whole organism application. Konopka et al. teach that "the delivery of functional ribozyme into cells by cationic liposomes is an inefficient process and needs extensive improvement before it can be used in *ex vivo* and *in vivo* applications (see abstract)." The specification as filed does not provide any guidance as to whole organism application other than injection of formulated VEGF-R-1 ribozyme into mice. The specification does not teach successful delivery of such ribozymes as evidenced by entry into the cell of interest and cleavage of the target VEGF-R. Further, note Crystal who teaches that mice models do not correlate to success in humans.

One of skill in the art would not accept on its face the successful delivery, and further treatment effects of the claimed catalyst compositions in whole organisms other than mice, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of such liposome -ribozyme compositions in whole organisms. Specifically the specification does not teach (1) stability of the ribozyme liposome composition *in vivo* in any whole organisms other than mice, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects via the catalytic molecule. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

5. Claims 16, 21-25, 27-34, 38, 47-48 and 60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 21-24 specify the function of the nucleic acid catalyst as decreasing the expression of RNA associated with any mammalian disease, a human disease, cancer, or inflammation. Claims 47-48 specify the biological system as a tumor or a mammalian eye.

Claims 16, 21-25, 27-34, 38 and 60 are drawn to pharmaceutical compositions (having an implied therapeutic application) and methods of treatment of a disease in a patient such as cancer or inflammation, and via systemic administration of the composition of claims 21.

The specification teaches delivery of liposomes (EPC-DOTAP:PEG) made by method (2) or ribozymes in saline (non-formulated) via intravitreal injection to mice. The specification further teaches EYPC(egg yolk PC):DOTAP-PEG C8 liposome delivery. The specification further teaches preparation and delivery to mice of EPC:CHOL (55:45), Shingomyelin (SM):EPC:CHOL (33:33:33), and EPC:CHOL:DODAC:PEG-Ceramide-C20 (50:25:15:10) (see Figure 9). Example 5 teaches the following formulations synthesized via method (1): EPC:CHOL:DODAC:PEG-ceramide-C20 (50:25:15:10), EPC:CHOL:DODAC:PEG-ceramide-C8 (50:25:15:10) and EPC:CHOL for injection into mice.

The instant claims 16, 21-25, 27-34, 38, 47-48 and 60 are drawn to pharmaceutical compositions, which imply whole organism treatment. Note Konopka et al. cited above who teach the unpredictability of ribozyme-liposomal delivery to whole organisms. The specification as filed does not provide any guidance as to the treatment of cancer or inflammation in a patient via administration of pharmaceutical compositions containing a formulated catalytic nucleic acid.

The instant claims 16, 21-25, 27-34, 38, 47-48 and 60 are further drawn to ribozyme-liposome compositions which decrease the amount of a target RNA associated with a disease. The specification as filed however provides no guidance as to the functional success of the VEGFR-R1 ribozyme in either cells in culture or whole organisms for the decreased expression of the target. Further, no correlation is taught between the application of such a ribozyme-liposome complex and association of the target with a disease condition. Therefore, it is not clear how one of skill in the art is to make and/or use the ribozyme composition for decreasing the amount of a target RNA associated with a disease in cells in culture or whole organisms.

One of skill in the art would not accept on its face the successful delivery, and further treatment effects of the claimed catalyst compositions in whole organisms other than mice, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of such liposome -ribozyme compositions in whole organisms. Specifically the specification does not teach (1) stability of the ribozyme liposome composition *in vivo* in any whole organisms other than mice, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects via the catalytic molecule. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error"

experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Holland et al. and Choi et al. (WO 96/10391) in view of Usman et al.

Claim 1 is drawn to a composition for facilitating delivery of a nucleic acid catalyst to a biological system, said composition having a PEG-ceramide conjugate, a lipid and a nucleic acid catalyst.

Holland et al. teach PEG-lipid conjugates (see page 2611) as components of liposomes and the interest in development of improved liposome delivery techniques based on application of PEG-lipid containing liposomes (see page 2616-2617). In columns 24 and 25 they teach the results of varying lengths of Ceramide chains on the fusogenic properties of the liposome (ie. To study the fusion capability of the liposome to a cell). The liposomes they teach contain components such as cholesterol, the lipid DOPE as well as phosphatidylcholine (PC) (see page 2614) and liposomes containing sphingomyelin, egg PC, and cholesterol (page 2616). In example

G they specifically teach liposomes composed of DOPE:cholesterol:DODAC:PEG-ceramide(C8) with the ratio 38:45:15:2 (col 24, lines 1-3). The fusogenic properties of these liposomes are compared to those having C14 and C20 length Ceramide in columns 24 and 25. Holland et al. do suggest the application of such liposomes for delivery of RNA, DNA or "therapeutic genes or oligonucleotides intended to induce or to block production of some protein within the cell (col. 12 lines 20-22)," which could consider ribozymes, but they do not exemplify delivery of specific nucleic acid catalysts via their liposomes *per se*.

Choi et al. (WO 96/10391) teach PEG-Cer liposomes designed for improved drug delivery of such liposomes such as reduced inhibition of RES uptake (see page 2) and/or optimized for reduced hydrolysis of the liposomes (see page 3). They teach liposomes having DSPC/PEG-Cer conjugated lipids also having cholesterol and/or Sphingomyelin (see pages 5 and 16). On pages 42-44 they teach optimization of DODAC PEG-Cer (C20) containing liposomes for prolonged circulation times where the concentration of PEG-Cer was 10% or 30%. Choi et al. do not teach liposomes having nucleic acid catalysts *per se*.

Usman et al. teach that "several groups have shown that delivery of cationic lipid-ribozyme complexes to cells in tissue culture can affect expression of target genes (p 253)."

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make a composition for delivery of a catalytic nucleic acid to a cell comprising a PEG-ceramide conjugate, a lipid and the nucleic acid catalyst because liposomal delivery of nucleic acid catalysts was known in the art as taught by Usman et al. and the addition

of PEG-ceramide to liposomal compositions was known in the art as taught by Holland et al. And Choi et al. for lowered fusogenic properties as taught by Holland et al., or for improved drug delivery and reduced hydrolysis of the liposomes as taught by Choi et al.

One of ordinary skill in the art would have been motivated to construct liposomes for delivery of catalytic nucleic acids to cells in culture or in vivo as taught by Usman et al. One of ordinary skill in the art would have been motivated to optimize such liposomes for delivery of catalytic nucleic acids to cells by the addition of PEG-cer conjugate for the benefits taught by Holland et al. and Choi et al. for reduced fusogenic properties or improved stability of the liposome.

One of ordinary skill in the art would have had a reasonable expectation of success to make liposomes having a PEG-ceramide conjugate, lipid and nucleic acid catalyst and further, delivery of said catalyst to a cell in culture, because many methods of liposome synthesis were known in the art (see Debs et al.), cationic liposomal delivery of ribozymes to cells was taught by Usman et al, and absent evidence to the contrary, addition of a PEG-ceramide conjugate to such liposomal compositions or alternatively, incorporation of a ribozyme into such liposomes as taught by Holland et al. or Choi et al. (so long as the charge ratio between the nucleic acid catalyst and the lipid components of the liposome were compatible) would have provided delivery of such a catalytic nucleic acid to a cell.

8. Claims 2-4, 9-15, 40-45, 49, 50, and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holland et al. and Choi et al. (WO 96/10391) and Usman et al. as applied to claim 1 above, and further in view of Choi et al. (U.S. Patent 5,820,873), Debs et al. and Wong et al.

Claims 2-4, 9-14, 40-45, 49, 50, and 61 are drawn to compositions for facilitating delivery of a nucleic acid catalyst to a biological system. The compositions comprise a PEG-ceramide conjugate, a lipid, and a nucleic acid catalyst. Dependent claims 2-4 further comprise, a phosphatidyl choline, cholesterol, or both. Claim 9 specifies the lipid as a cationic lipid. Claims 10 and 11 specify the lipid as DODAC or DOTAP. Claims 12-14 and 49 specify the PEG-Ceramide conjugate as a fatty acid of 8, 14 or 20 carbons, or between 6 and 20 carbons (claim 49). Claim 15 specifies the phosphatidyl choline as egg yolk phosphatidyl choline. Claims 40-41 specify formation of the compositions of claims 1-4 via a reverse phase evaporation process or the Bligh and Dyer extraction method. Claims 42-44 specify the concentrations of the lipid as 0-30%, 5-30%, or 15%. Claim 45 specifies 50% egg yolk phosphatidyl choline, 25% cholesterol, 15% lipid, and 10% PEG-Ceramide conjugate. Claims 50 and 61 further specify a composition having a PEG-Cer, phosphatidylcholine, cholesterol and nucleic acid catalyst or a non-cationic lipid, a cationic lipid, PEG-Cer and nucleic acid catalyst.

Choi et al. (U.S. Patent 5,820,873) also teach PEG-Cer liposomes having C8, C14, C16, and C24 length ceramide molecules (col. 12) and evidence of higher blood/liver ratios in mice with the C20 Cer-liposomes and the lowest ratio with the C8 Cer-liposomes (Col. 24).

Debs et al. teach optimization of liposomes for transgene delivery to organisms such as cationic or anionic liposomes and having a lipid composition of between 5%-100%, including lipids such as DOTAP (see columns 17 and 18), and addition of PC and cholesterol. They further teach the reverse phase evaporation method and other common methods known in the art for liposome synthesis (col. 18, line 33).

Jaasekelainen et al. teach applications of antisense oligonucleotides to cells in culture via cationic liposome delivery. They teach DOTAP and DOTMA and EPC containing liposomes of different ratios.

Wong et al. teach formation of cationic liposomes via the Bligh and Dyer. Specifically they teach formation of DODAC/DNA hydrophobic complex.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to construct PEG-ceramide, lipid and nucleic acid catalyst containing liposomes as taught supra, for example, having lipid:cholesterol:PEG-Cer of 50:445:5 as taught by Choi et al. (Col. 3, lines 30) or DOPE/DODAC/PEG-Cer (C20) in 75:15:10 ratio (Choi et al. Col. 4, line 14), etc., and further, to optimize such compositions by application of known lipid combinations in the art, including type of lipid used and % of each lipid (see Debs et al.), and further, optimization of the PEG-ceramide content of such liposomes because such modulations were known in the art (see Choi et al. who teach modification of the ceramide length for improved delivery of the liposomes). Further, absent evidence to the contrary, it would have been prima facie obvious to make such PEG-ceramide, lipid and nucleic acid catalyst containing

liposomes via methods well-known in the art such as the reverse phase method (see Debs et al.) or the Bligh and Dyer method (see Wong et al.).

One of ordinary skill in the art would have been motivated to make a liposome containing a PEG-Cer/lipid/catalytic nucleic acid complex as taught supra, and further, to optimize delivery of such complexes to cells by modulation of commonly known parameters in the liposome construction art such as amounts of: (1)phosphatidyl choline and/or cholesterol as taught by Choi et al. for example, (2) a cationic lipid as taught by Usman for delivery of a catalytic nucleic acid, (3) specific lipids known in the art such as DODAC or DOTAP, as taught by Holland et al (see col. 8, para. 2), (4) 8C, 14C, 20C or 6-20C ceramide length as taught by Choi et al., (5) 5%-100% lipid composition as taught by Debs et al. and/or (6) cationic compositions as taught by Jaasekelainen et al.

One of ordinary skill in the art would have had a reasonable expectation of success to make a liposomal composition for delivery of a catalytic nucleic acid to a cell having combinations of the above components because liposome construction via the reverse phase or Bligh and Dyer methods is well known in the art (see Debs et al. and Wong et al.). Further, one of ordinary skill in the art would have had a reasonable expectation of success to apply known liposomal modifications as taught by Choi et al. in light of Holland et al. and Debs et al. for optimized delivery of catalytic nucleic acid containing ribozymes as taught by Usman et al. because absent evidence to the contrary, it would have been expected that said modifications would perform the

intended optimized function as taught in the art, for example, addition of PEG-Cer would have been expected to lower the fusogenic property of the liposome, etc.

9. Claims 5-8, 26, 35-37, 39, 46 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holland et al. and Choi et al. (WO 96/10391) and Usman et al. as applied to claim 1 above, and further in view of Bennett et al., Zaia et al. and the combination of Janjic et al. with Draper and McSwiggen.

Claims 5-8, 35-37 and 48 are drawn to compositions for facilitating delivery of a nucleic acid catalyst to a biological system. The compositions comprise a PEG-ceramide conjugate, a lipid, and a nucleic acid catalyst. Dependent claims 5-8 specify the nucleic acid having endonuclease activity, comprising one or more ribonucleotides or deoxyribonucleotides, or a hammerhead motif.

Claim 35 specifies a chemically modified catalyst. Claims 36-37 are drawn to a catalyst for cleaving VEGF-R RNA such as VEGF-R-1. Claim 46 specifies the nucleic acid catalyst encoded by a vector. Claims 47-48 specify the biological system as a tumor or a mammalian eye. Claims 50 and 61 further specify a composition having a PEG-Cer, phosphatidylcholine, cholesterol and nucleic acid catalyst or a non-cationic lipid, a cationic lipid, PEG-Cer and nucleic acid catalyst. Claim 26 is drawn to delivery of the ribozyme-liposome complex to the cell.

Bennett et al. teach liposome antisense oligonucleotide compositions with DOTMA as the cationic lipid and the oligonucleotides having phosphorothioate backbones. They teach enhanced cellular uptake and activity of phosphorothiate antisense oligonucleotides when using cationic lipids.

Janjic et al. teach the role of VEGF cancer and angiogenesis, the importance of VEGF receptors in the development of blood vessels and evidence that VEGF and its receptors contribute to tumor growth. They further teach studies by others employing antisense to antibodies directed against VEGF for the elucidation of such functions of VEGF. They further teach development of VEGFR ligand antagonists.

McSwiggen teaches a method for determining a suitable target site of an intended RNA target for design of a ribozyme having the antisense to that target site.

Draper teaches a method of selection for a ribozyme having a defined RNA target site, and further expression of such a functional ribozyme from a vector.

Zaia et al. teach ribozymes as functional equivalents, a "second generation" of antisense molecules.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to construct PEG-ceramide, lipid and nucleic acid catalyst containing liposomes as taught *supra*, and specifically, for said catalytic nucleic acid to have endonuclease activity, contain ribonucleotides or deoxyribonucleotides, form a hammerhead motif, contain chemical modifications, target VEGF RNA such as the ribozyme VEGF-R-1, or be expressed

from a vector becuase Bennett et al teach the feasible delivery of oligonucleotides via liposomes to cells (see also Usman who teaches delivery specifically of ribozymes to cells as discussed supra), and further Janjic et al. teach the desired inhibition of VEGF and Draper and McSwiggen teach methods for design of ribozyme catalysts to an intended target such as VEGF.

One of ordinary skill in the art would have been motivated to make a catalytic nucleotide containing PEG-ceramide liposome as taught supra, and further to deliver in general catalytic nucleotides such as ribozymzes as taught by Usman (note, Usman teaches chemically modified ribozymes having endonuclease activity and specific designs of ribozymes such as the hammerhead motif), and further for inhibition of a target in a cell (such as antisense inhibition taught by Bennett et al.). One of ordinary skill in the art would have been motivated to deliver via such liposomes any such ribozyme, and in the instant case one designed to inhibit VEGF because Janjic et al. teach the motivation for inhibition of VEGF via antisense and antibodies, it was known in the art at the time the invention was made that ribozymes were functional equivalents of antisense (Zaia teaches them as a "second generation" of antisense).

One of ordinary skill in the art would have had a reasonable expectation of success to make a PEG-Ceramide/lipid/ catalytic nucleotide containing liposome because the individual components of such liposomes were well known in the art as discussed supra. Specifically, one of ordinary skill in the art would have had a reasonable expectation of success to (1) make a ribozyme to target VEGF via the methods of Draper and /or McSwiggen, (2)substitute a ribozyme catalytic nucleic acid for VEGF into the liposomes taught by Usman et al, (3) optimize

such liposomes as taught supra, for variation of charge and lipid content and further by addition of a PEG-ceramide component for the study of optimized delivery of such liposomes, and further (4), synthesize such liposomes by any one of a number of well known techniques in the art such as the reverse phase evaporation or Bligh and Dyer techniques as taught by Debs et al. and Wong et al.(as taught supra).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *George Elliott, Ph.D.* may be reached at (703) 308-4003. The examiner's primary, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

NANCY DEGEN
PRIMARY EXAMINER